REMARKS

Claims 1-31 were previously pending in the application. Claims 1, 8, 13, 17-19 and 23-24 have been amended. Claims 2-5, 7, 9-11, 14-16, 20-22 and 25-31 have been canceled. Accordingly, upon entry of the amendments presented herein, claims 1, 6, 8, 12-13, 17-19, 23-24 will remain pending in the application.

No new matter has been added.

Claims 1, 8, 17-19 and 23-24 have been amended to replace the term "CDK inhibitor" with the term "roscovitine, or an enantiomer thereof" and to specify that the metabolite of 1-(2-C-cyano-2-dioxy-β-D-arabino-pentofuranosyl)-N4-palmitoyl cytosine is 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine. Support for these amendments can be found at least, for example, in former claims 4 and 5 and on page 9, lines 1-6 of the application as filed. Finally, claims 13 and 17 have been amended in order to specify that the proliferative disorder is selected from lung cancer, prostate cancer, bladder cancer, head and neck cancer, colon cancer, sarcoma and lymphoma. Support for these amendments can be found at least, for example, on page 5, lines 22-24 of the application as filed.

The foregoing claim amendments have been made *solely for the purpose of expediting prosecution* of the present application and should in no way be construed as acquiescence to any of the Examiner's rejections in this or in any other Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another related application.

In view of the foregoing claim amendments and the arguments set forth below, Applicants respectfully submit that the claims are now in condition for allowance.

Claim Objections – 35 USC § 101

Claims 7 and 28-31 are rejected under 35 USC § 101. Applicants respectfully disagree, but note that claims 7 and 28-31 have been canceled, thereby rendering this objection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims under 35 USC § 101.

Claim Rejections – 35 USC § 112

Claims 7 and 28-31 are rejected as indefinite under 35 USC § 112, for reciting a use without any active, positive steps delimiting how this use is actually practiced. Applicants respectfully disagree. However, *solely to expedite prosecution*, claims 7 and 28-31 have been canceled, thereby rendering the rejection moot.

Claims 1-4, 6-15, 17-26 and 28-31 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner rejects reference to "metabolites" of 1-(2-C-cyano-2-dioxy-β-D-arabino-pentofuranosyl)-N4-palmitoyl cytosine as too broad and undefined. Applicants respectfully disagree. However, *solely to expedite prosecution*, the claims have been amended to specify that the claimed metabolite is 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine.

Claims 1, 2, 5-9, 12-20 and 23-26 and 29-31 are rejected under 35 USC § 112, first paragraph, on the ground that the specification does not reasonably provide enablement for methods comprising the use of all possible CDK inhibitors. Applicants respectfully disagree. However, *solely to expedite prosecution*, the claims have been amended to substitute the term "CDK inhibitor" with the term "roscovitine."

Claims 1-4, 6-15, 17-26 and 28-31 are rejected under 35 USC § 112, first paragraph, on the ground that the specification does not reasonably provide enablement for methods comprising the use of all possible metabolites of 1-(2-C-cyano-2-dioxy-β-D-arabino-pentofuranosyl)-N4-palmitoyl cytosine. Applicants respectfully disagree. However, *solely to expedite prosecution*, the claims have been amended to specify that the claimed metabolite is 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine.

Claims 1-31 are rejected under 35 USC § 112, first paragraph, on the ground that the specification does not reasonably provide enablement for methods and compositions comprising a method of treating any cancer whatsoever, or any proliferative disorder whatsoever. The Examiner states that the specification, "while being enabling for a method of treating certain specific cancers such as colon, lung and prostate cancer, does not reasonably provide enablement for…method[s] of treating any cancer whatsoever or any proliferative disorder whatsoever." Applicants respectfully disagree. However, *solely to expedite prosecution*, the claims have been

amended to specify that the proliferative disorder is selected from lung cancer, prostate cancer, bladder cancer, head and neck cancer, colon cancer, sarcoma and lymphoma.

For at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejections of claims under 35 USC § 112.

Claim Rejections – 35 USC § 103

Claims 1-4, 6-15, 17-26 and 28-31 are rejected under 35 USC § 103(a) as being unpatentable over Kameko *et al.* (U.S. Patent No. 5,691,319) in view of Altieri *et al.* (WO 03/039536. The Examiner asserts that it would have been obvious for one of ordinary skill in the art at the time of the invention to administer both 1-(2-C-Cyano-2-deoxy-β-D-arabino-pentafuranosyl)-cytosine (CNDAC), as described by Kameko *et al.*, and a CDK inhibitor such as roscovitine, as described by Altieri *et al.*, to a patient suffering from cancer, in a composition comprising a pharmaceutically acceptable carrier. The Examiner further asserts that one would be motivated to do so because both compounds are used for the treatment of cancer, and that one would reasonably expect success because multidrug regimens are commonplace.

Applicants respectfully disagree. The present claims are directed toward a combination of roscovitine and 1-(2-C-cyano-2-dioxy-β-D-arabino-pentofuranosyl)-N4-palmitoyl cytosine, which is useful for treating proliferative disorders, particularly cancer. With regard to the above rejection, Applicants contend that there is no teaching or suggestion in Kameko *et al.* that the compounds disclosed therein could be administered in combination with a CDK inhibitor, let alone the specific CDK inhibitor roscovitine. This deficiency is not cured by Altieri *et al.*, who discloses combination treatment with at least one compound that arrests cell mitosis and at least one compound that inhibits survivin function (*e.g.* roscovitine). One of skill would not be motivated to combine the teachings of the cited art because there is no teaching or suggestion in either reference that the compounds disclosed by Kameko *et al.* would be capable of arresting cell mitosis. As such, the presently claimed combination therapy is not obvious in view of the Kameko and Altieri references, alone or in proper combination.

The above argument notwithstanding, even if the skilled practitioner were to consider combining the teachings of Kameko *et al.* with Altieri *et al.* (which they would not), there would be no reason to expect that roscovitine and 1-(2-C-cyano-2-dioxy-β-D-arabino-pentofuranosyl)-N4-palmitoyl cytosine (or metabolite) would combine synergistically. Instead, the skilled

practitioner would understand that whether or not two pharmacologically active agents interact synergistically is entirely unpredictable.

By way of evidence, Applicants enclose herewith supplemental data, in the form of an Inventor Declaration filed under 35 USC § 1.132 , which supports the presence of a synergistic effect between seliciclib (R-roscovitine) and CNDAC. In both H460 and H358 cell lines, the combination of both agents generated a greater number of cells with a sub-G1 DNA content (apoptotic cells) than either of the single agent treatments. This effect was synergistic (*i.e.* greater than the sum of the effects of individual agents), particularly when the CNDAC treatment preceded the seliciclib treatment (CNDAC/sel).

Accordingly, because the combination of seliciclib and CNDAC exhibits greater than expected results [MPEP § 716.02(a)], the instant claims are not obvious in view of Kameko *et al.* in combination with Altieri *et al.*

For at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejections of claims under 35 USC § 103(a).

Claims 1-31 are rejected under 35 USC § 103(a) as being unpatentable over Hanaoka *et al.* in view of Altieri *et al.* The Examiner asserts that it would have been obvious for one of ordinary skill in the art at the time of the invention to administer either CNDAC or CS-682, as described by Hanaoka *et al.*, in combination with a CDK1 antagonist such as roscovitine, as described by Altieri *et al.*, to a patient suffering from cancer. The Examiner further asserts that one would be motivated to do so because both compounds are used for the treatment of cancer, and that one would reasonably expect success because multidrug regimens are commonplace.

Applicants respectfully disagree. As discussed above, the present claims are directed toward a combination of roscovitine and 1-(2-C-cyano-2-dioxy-β-D-arabino-pentofuranosyl)-N4-palmitoyl cytosine, which is useful for treating proliferative disorders, particularly cancer. The problem is solved by the presently claimed combination of roscovitine and 1-(2-C-cyano-2-dioxy-β-D-arabino-pentofuranosyl)-N4-palmitoyl cytosine. With regard to the above rejection, Applicants contend that there is no teaching or suggestion in Hanaoka *et al.* that the compounds disclosed therein could be administered in combination with a CDK inhibitor, let alone the specific CDK inhibitor roscovitine. Neither would the skilled practitioner find guidance in Altieri *et al.*, who discloses combination treatment with at least one compound that arrests cell mitosis and at least one compound that inhibits survivin function (*e.g.* roscovitine). One of skill

would not be motivated to combine the teachings of the cited art because there is no teaching or suggestion in either reference that the compounds disclosed by Hanaoka *et al.* would be capable of arresting cell mitosis. In fact, Hanaoka *et al.* teach a mechanism of action of CNDAC and CS-682 that involves incorporation into the DNA of tumor cells, and the induction DNA self-strand breakage. Notably, this mechanism does not involve the arrest of cell mitosis. As such, the presently claimed combination therapy is not obvious in view of the Hanaoka and Altieri references, alone or in proper combination.

Notwithstanding the above argument, even if the skilled practitioner were to consider combining the teachings of Hanaoka *et al.* with Altieri *et al.* (which they would not), there would be no reason to expect that roscovitine and 1-(2-C-cyano-2-dioxy-β-D-arabino-pentofuranosyl)-N4-palmitoyl cytosine (or metabolite) would combine synergistically (See discussion of synergistic effect described above).

For at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejections of claims under 35 USC § 103(a).

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

An extension of time and appropriate fee is being filed herewith. If any additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. CCI-066US from which the undersigned is authorized to draw.

Dated: November 6, 2009

Respectfully submitted,

Electronic signature: /Brian C. Trinque, Ph.D./
Brian C. Trinque, Ph.D.
Registration No. 56,593
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicants